Hindawi Publishing Corporation
Journal of Chemistry
Volume 2013, Article ID 895892, 5 pages
http://dx.doi.org/10.1155/2013/895892

Research Article

Synthesis, Characterization, and Agricultural Biological Activities of 5-Fluoro-2-hydroxy Butyrophenone

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Received 17 March 2013; Revised 6 May 2013; Accepted 13 May 2013

Academic Editor: Stojan Stavber

A novel synthetic approach towards 5-fluoro-2-hydroxy butyrophenone is reported. Using 4-fluorophenol as a raw material, the processes of etherification protection, Friedel-Crafts acylation and demethylation provide the target compound under mild conditions. The structure was characterized by the melting point and IR, MS, ^{1}H-NMR, and ^{13}C-NMR spectroscopy. The bioassay results indicate that the target compound exhibits potent antifungal activities against *Valsa mali*, *Coniella dipodiella*, and other agricultural plant fungi. The target compound also shows potent herbicidal activities for *Lactuca sativa*, a dicotyledon, and *Echinochloa crusgalli*, a monocotyledon. The toxicity regression C_{50} values of the compound against *Valsa mali*, *Coniothyrium diplodiella*, *Lactuca sativa* seedling, and *Echinochloa crusgalli* seedling were calculated by SPSS. The Hormesis effect for roots of *Echinochloa crusgalli* was confirmed.

1. Introduction

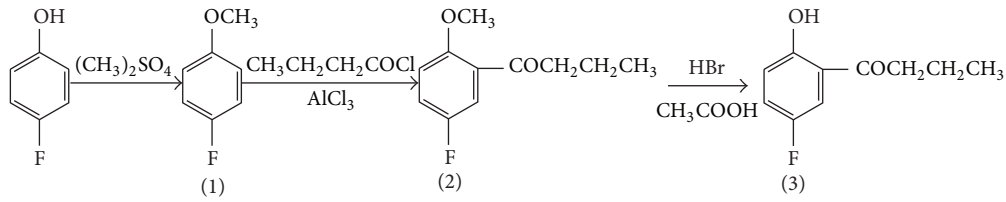
As one of the most important classes of allelochemicals, phenols show wide biological activity to living organisms [1, 2]. Because of their natural occurrence, biological activity, and industrial applications, extensive attention has been paid to prepare new derivatives by chemical modification and to explore the new application of phenols. For example, the Research Center of Agricultural Bionic Engineering & Technology of Shandong Province found that 2-hydroxyphenyl-1-butanone, that is, 2-(1-butanoyl) phenol can effectively control *Valsa mali*, *Coniella diplodiella*, (Speg.) and other plant pathogenic fungi and thus carried out further research into developing a new fungicide [3].

Some special features, such as electronic effect, block effect, mimic effect, and lipid permeability effect, usually make fluorine-containing agricultural chemicals highly effective against pests, weeds, and fungi, and they have been attracting researchers from all over the world [4–6]. Until now, it has not been possible to accurately predict the bioactivity change when substituting atoms with a fluorine-containing group. More experimental research is needed to confirm how and where to introduce fluorine-containing atoms to maximize their impact.

The principal objective of this research is to prepare 5-fluoro-2-hydroxy butyrophenone, that is, 4-fluoro-2-butanoyl phenol, and investigate its agricultural biological activities. To the authors' knowledge, the agricultural bioassay of 5-fluoro-2-hydroxy butyrophenone has not been reported so far. Few papers have been published on the preparation of 5-fluoro-2-hydroxy butyrophenone, as well as its identification spectra.

The target compound is classified as 2-hydroxy-phenyl ketones which are usually prepared by a Fries rearrangement reaction of a phenolic ester, an intermediate obtained by hydroxyl acylation of a phenol [7]. The strong electron withdrawing of the fluorine atom makes it difficult to change 4-fluoro phenolic ester to 5-fluoro-2-hydroxyphenyl ketone. In Suter et al.'s paper [8], the target compound was prepared by the Fries rearrangement reaction at 150°C, with aluminium trichloride existing as a catalyst. Kindler and Oelschläger [9] synthesized the compound at 150°C, taking 4-fluorine phenol and n-butanoic acid as raw materials, and boron trifluoride as a catalyst. Both methods require a high reaction temperature, and the latter needs a costly boron trifluoride.

In this study, 5-fluoro-2-hydroxy butyrophenone was prepared from the starting material 4-fluorophenol, by the sequential reactions of hydroxyl protection, acylation, and final



Scheme 1: Synthetic route of 5-fluoro-2-hydroxy butyrophenone.

demethylation to overcome the disadvantages previously mentioned. Scheme 1 shows the experimental synthesis route. Taking cost factors into consideration, 4-fluoroanisole should be manufactured by other more effective route or bought from the marketplace. It can be directly used as the starting material in future production of 5-fluoro-2-hydroxy butyrophenone on an industrial scale. The synthetic route may be referenced by other studies into the preparation of carbonyl phenols p-substituted by a strong electron-withdrawing group.

2. Experimental

2.1. Materials and Instrumentation. Anhydrous aluminium trichloride, 4-fluorophenol, dimethyl sulfate, n-butyryl chloride, hydrobromic acid, and other reagent-grade chemicals were commercially available and were used without further purification. Cyprodinil (Syngenta, 50% WDG) and Pyrazosulfuron-ethyl (Shenzhen Sunrising Industry Co., Ltd, 10% WP) were used as reference fungicide and herbicide, respectively.

Valsa mali and *Coniothyrium diplodiella* were obtained from the Research Center of Agricultural Bionic Engineering & Technology of Shandong Province. *Lactuca sativa*, with the brand of Lisheng, was bought from a seed firm. *Echinochloa crusgalli* was collected from the campus of Qingdao Agricultural University which was not contaminated by any herbicides. The fungi and plant material specimen has been deposited in the Research Center of Agricultural Bionic Engineering & Technology of Shandong Province.

^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker AV-500 spectrometer. Chemical shifts were reported in ppm relative to tetramethylsilane (TMS), and multiplicities are given as s (singlet), d (doublet), t (triplet), q (quartet), or m (multiplet). The solvent for NMR spectra was $CDCl_3$. MS spectrum was determined by a Bruker ESI spectrometer, and signals were given in m/z. IR spectra were investigated by KBr pellet method for solid sample or liquid film method for liquid sample and recorded in the range of 450–4000 cm^{-1} by Fourier transform infrared (FTIR) spectroscopy. Melting point was obtained on a WRS-1A numeral melting point apparatus.

2.2. Synthesis

*2.2.1. 4-Fluoroanisole (**1**).* To a toluene solution (30 mL) of 4-fluorophenol (22.4 g, 0.2 mol) was added an aqueous solution (50 mL, 15%) of sodium hydroxide. The reaction mixture was stirred at 10~20°C for 0.5 h. To the mixture, dimethyl sulfate (24.62 mL, 0.26 mol) was added dropwise in 2 h. The mixture was heated to 40°C, stirred at the same temperature for 2 h, and then cooled to room temperature. The water phase was extracted with ethyl acetate (10 mL × 3). The combined organic phase was washed with water (20 mL × 2), dried by anhydrous sodium sulfate, and evaporated at 45°C under vacuum to provide **1**, as a lightly yellow liquid (22.83 g), in 90.59% yield. Using a thin plate of silicate gel GF 254 and petroleum ether-ethyl acetate system (7 : 1, by volume) as a developing agent, RF values of 0.22 and 0.657 were obtained for 4-fluorophenol and **1**, respectively.

*2.2.2. 5-Fluoro-2-methoxy Butyrophenone (**2**).* Under anhydrous conditions, the mixture of n-butyryl chloride (15 mL) and anhydrous aluminium trichloride (44.06 g, 0.33 mol) in carbon disulfide (90 mL) was stirred for 1 h, **1** (13.86 g, 0.11 mol) was introduced dropwise in 2 h at 0°C. Then reaction mixture was stirred for 4 h at 50°C. After solvent evaporation under reduced pressure, the residue was treated with 4%~6% hydrochloric acid solution, extracted with benzene (10 mL × 3), and the organic phase obtained was washed with water (20 mL × 2), dried with anhydrous sodium sulfate, and distilled under reduced pressure to give **2** (12.75 g), as a slightly yellow liquid, in 59.14% yield. TLC analysis was performed upon a thin plate of silicate gel GF 254, and the Rf values for **1** and **2** were found to be 0.657 and 0.760, respectively according to the developing agent of petroleum ether-ethyl acetate system (7 : 1, by volume).

*2.2.3. 5-Fluoro-2-hydroxy Butyrophenone (**3**).* To a mixture of **2** (11.76 g, 0.06 mol) and glacial acetic acid (40 mL) was added hydrobromic acid dropwise (15 mL) at refluxing temperature; then, the resulting mixture was refluxed for 10 h. The reaction mixture was treated with slight excess of a dilute sodium hydroxide; then, the pH value was adjusted to 3~4 with 10%~15% sulfuric acid solution. This mixture was cooled by the ice-water bath to afford **3** as a slightly yellow crystalline in 61.72% yield. TLC analysis was carried out by a thin plate of silicate gel GF 254, and the Rf values for **2** and **3** were found to be 0.760 and 0.561, respectively, using the developing agent, of petroleum ether-ethyl acetate system (7 : 1, by volume).

2.3. Bioassays

2.3.1. Antifungal Assay. The mycelium growth rate test [10] was used to investigate the inhibition effects of 5-fluoro-2-hydroxy butyrophenone on six popular plant pathogenic fungi. The in vitro test was contacted in Petri dishes, 6.0 cm in diameter. 5-fluoro-2-hydroxy butyrophenone was dissolved

in acetone and added to PDA medium (potato 200 g, dextrose 20 g, and agar 17 g litre^{-1}) immediately before it was poured into the Petri dishes at 40–45°C. Compound **3** was tested at 100, 50, 25, 12.5 and 6.25 mg·L^{-1} against *Valsa mali* but at the double doses against *Coniothyrium diplodiella*. Three replicate plates were used at each concentration. The control received the same quantity of acetone mixed with PDA. The disks of mycelia felt (4 mm diameter) of the pathogenic fungi taken from 7-day-old cultures on PDA plates were inoculated aseptically to the center of Petri dishes. The treatments were incubated at 25°C. Colony growth diameter was measured when the fungal growth in the control treatments had just completely covered or was about to cover the Petri dishes. Antifungal activity was expressed in terms of percentage of mycelium growth inhibition calculated from the following formula:

$$\text{mycelium growth inhibition} = \left[\frac{(d_c - d_t)}{(d_c - 4)}\right] \times 100, \quad (1)$$

where d_c and d_t are average diameters in mm of fungal colonies of control and treatment, respectively.

The multiple compare of the inhibition of the test compound against various fungi was carried out by Duncan's method with statistical analysis software—SPSS 15.0. The EC_{50} values were estimated with the same software based on probit analysis.

2.3.2. Herbicidal Assay. The herbicidal activity of 5-fluoro-2-hydroxy butyrophenone was evaluated using a previously reported procedure [11]. The receptor plants' seeds were sterilized with 2% sodium hypochlorite solution for 15 minutes, washed with distilled water, dipped in running tap water for 5 h was placed on the moistened papers, and then put into a plant incubator for germination. The acrospire was allowed to grow to 2-3 mm, before it was inserted into a PPA medium (agar 5 g·L^{-1}). Stock solution of 5-fluoro-2-hydroxy butyrophenone was prepared in acetone at a concentration of 50000 mg·L^{-1} and then diluted to the required test concentrations. Three replicate cups were used at each concentration. The control received the same quantity of acetone mixed with PPA.

The sprouting seeds were planted into the PPA medium in a cup of 25 mL. The treatments were maintained at a plant incubator for 2–5 days, at 25°C and relative humidity 60%. The root length and hypocotyl length were measured when the root was about to touch the cup bottom. The herbicidal activity on test weeds was evaluated by the inhibition rate calculated as follows:

$$\text{root growth inhibition} = \frac{(L_c - L_t)}{(L_c - 2)} \times 100,$$
$$\text{hypocotyl growth inhibition} = \frac{(L_c - L_t)}{L_c \times 100}, \quad (2)$$

where L_c and L_t are average diameters in mm of root length or hypocotyl length of control and treatment, respectively.

The EC_{50} values were calculated using SPSS 15.0 based on probit analysis.

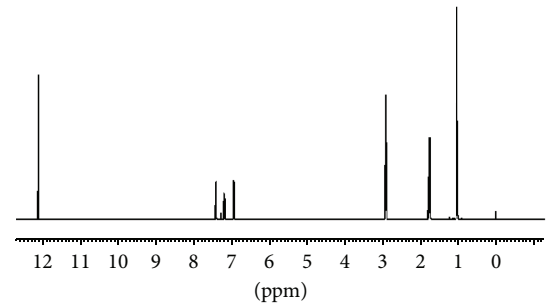


Figure 1: ^{1}H-NMR spectra of 5-fluoro-2-hydroxy butyrophenone.

3. Results and Discussion

3.1. Characterization of Compounds

*3.1.1. 4-Fluoroanisole (Compound **1**).* IR (KBr, $\bar{\nu}$, cm^{-1}): 3076 (ν: Ar C–H), 2966 ($\nu_{as:-CH3}$), 1604 (ν: $Ar_{C=C}$), 1153 ($\nu_{as:C-F}$), 1036 ($\nu_{:C-F}$), and 830 (γ: Ar_{C-H}, assigned to 1,4-disubstituted phenol ring). ^{1}H-NMR (500 MHz, $CDCl_3$), δ (ppm): 6.96~7.01 (2H, m, Ar–H), 6.81~6.88 (2H, m, Ar–H), 3.78 (3H, s, CH_3).

*3.1.2. Preparation of 5-Fluoro-2-methoxy Butyrophenone (Compound **2**).* IR (KBr, $\bar{\nu}$, cm^{-1}): 2971 (ν: Ar C–H), 2941 ($\nu_{as:-CH3}$), 1715 ($\nu_{:C=O}$), 1220 ($\nu_{as:C-O-C}$), 1096 ($\nu_{as:C-F}$), 1040 ($\nu_{:C-F}$), and 832 (γ: Ar_{C-H}, assigned to 1,2,4-trisubstituted phenyl). ^{1}H-NMR (500 MHz, $CDCl_3$), δ (ppm): 7.52~7.55 (1H, dd, Ar–H), 7.22~7.26 (1H, m, Ar–H), 6.97~7.02 (1H, dd, Ar–H), 3.78 (3H, s, CH_3), 2.92~2.94 (2H, t, $-CO-CH_2-$), 1.75~1.82 (2H, m, $-CH_2-$), 1.01~1.04 (3H, t, $-CH_3$).

*3.1.3. 5-Fluoro-2-hydroxy Butyrophenone (Compound **3**).* The melting Point was 37.8~38.3°C, which is in good agreement with 38~39°C reported in research papers [8, 9]. IR (KBr, $\bar{\nu}$, cm^{-1}): 3444 ($\nu_{:OH}$), 2968 ($\nu_{as:-CH3}$), 1650 ($\nu_{:C=O}$; ν: $Ar_{C=C}$), 1585 (ν: $Ar_{C=C}$), 1488 (ν: $Ar_{C=C}$), 1384 ($\nu_{as:-CH3}$), 1130 ($\nu_{as:C-F}$), 994 ($\nu_{:C-F}$), and 857 (γ: Ar_{C-H}, assigned to 1,2,4-trisustituted phenol ring). ESI-MS, M^+: m/z 183.0. ^{1}H-NMR (500 MHz, $CDCl_3$), δ (ppm): 12.12 (1H, s, Ar–OH, forming intramolecular hydrogen bond with ortho-position C=O), 7.41~7.43 (1H, dd, Ar–H), 7.18~7.22 (1H, m, Ar–H), 6.93~6.96 (1H, dd, Ar–H), 2.91~2.94 (2H, t, $-CO-CH_2-$), 1.74~1.82 (2H, m, $-CH_2-$), and 1.01~1.05 (3H, t, $-CH_3$). ^{13}C-NMR (500 MHz, $CDCl_3$), δ (ppm): seven signal peaks in the low field regions, 205.84 (C=O), 158.66 (Ar), 155.73 (Ar), 123.64~123.84 (d, Ar), 119.76~119.82 (d, Ar), 118.79~118.84 (d, Ar), and 114.76~114.95 (d, Ar); three signal peaks were found in the high field regions, 40.27 ($-CH_2-$), 17.68 ($-CH_2-$), and 13.75 (CH_3). The spectra of ^{1}H-NMR and ^{13}C-NMR are shown in Figures 1 and 2, respectively.

The yield of the final target compound is 33.1% in our mild synthesis route, which is lower than that of Fires rearrangement approach at 150°C (70.6%) [8] and that of catalytic method using costly boron trifluoride (79.7%) [9]. The ideal preparation method needs continual investigating. We will report the related research in another paper.

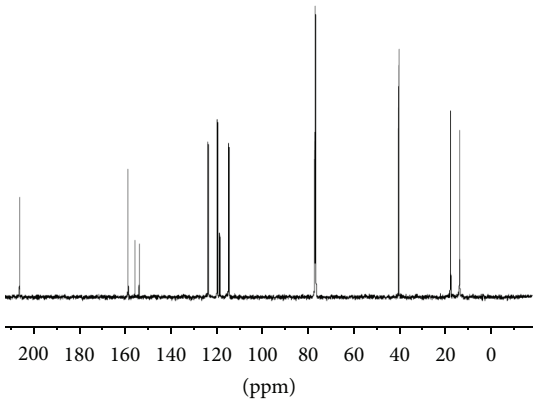


Figure 2: ^{13}C-NMR spectra of 5-fluoro-2-hydroxy butyrophenone.

Table 1: Antifungal activity of 5-fluoro-2-hydroxy butyrophenone against six plant pathogenic fungi.

Fungus	Mycelial growth inhibition (%)[#]
Fusarium graminearum Sehw	41.6[c]
Valsa mali	79.0[a]
Fusarium oxysporum f. *vasinfectum*	25.0[f]
Coniella diplodiella	66.0[b]
Fusarium oxysporum f. sp. *cucumerinum*	36.6[d]
Alternaria brassicae	27.9[e]

[#]Mycelial growth inhibition percentages within a column followed by the same letter are not significantly different ($P < 0.05$).

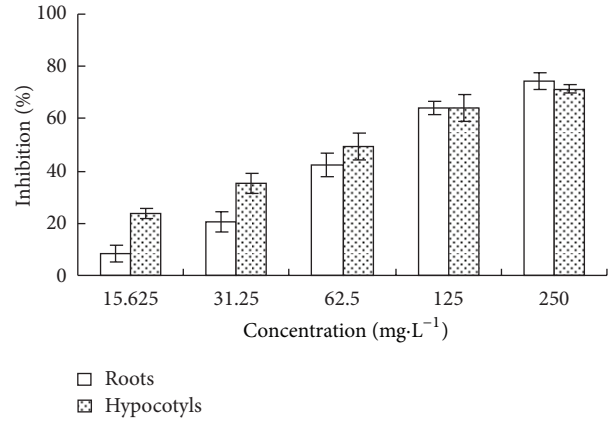


Figure 3: Bioassay of 5-fluoro-2-hydroxy butyrophenone on the seedling growth of *Lactuca sativa* L.

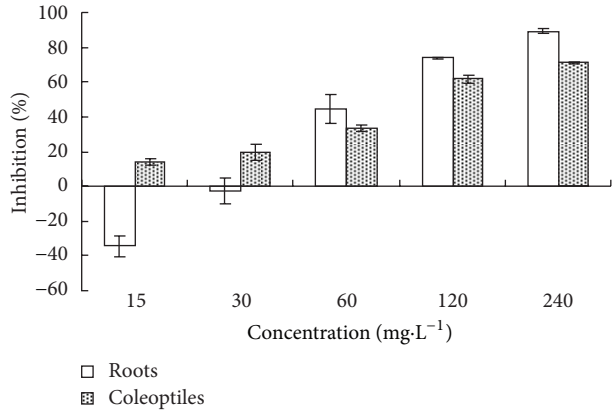


Figure 4: Bioassay of 5-fluoro-2-hydroxy butyrophenone on seedling growth of *Echinochloa crusgalli*.

3.2. Agricultural Biological Activities of Compound **3**

3.2.1. Antifungal Activity against Six Plant Pathogenic Fungi. Compound **3** was tested for its antifungal activity against six fungi species at 100 mg litre^{-1}. Table 1 shows that the compound exhibits antifungal activity against the test fungi with different sensitivities. It also shows the strongest activity against Valsa mali and *Coniella diplodiella* and the lowest antifungal activity against *Fusarium oxysporum f. Sp. vasinfectum* and Alternaria brassicae.

As shown in Table 2, 5-fluoro-2-hydroxy butyrophenone displays good fungicidal activity against Valsa mali and Coniothyrium diplodiella, and the EC_{50} values were 31.46 and 58.62 mg·L^{-1}, respectively. The antifungal activity of the compound against Valsa mali and Coniothyrium diplodiella is weaker than that of Cyprodinil, which showed EC_{50} values of 10.4 and 10.2 mg·L^{-1}, respectively.

3.2.2. Inhibition against the Seedling of 2 Plants. The growth inhibition was clearly observed on the roots and hypocotyls of *Lactuca sativa* seedlings at the concentration of 15.625 mg·L^{-1}. As shown in Figure 3, the lengths of both roots and hypocotyls decreased as the concentration increased.

As seen from Figure 4, the inhibition was evident on hypocotyls of *Echinochloa crusgalli* at the concentrations of compound **3** from 15 mg·L^{-1} to 240 mg·L^{-1} and the instances of low promote and high restrain; that is, Hormesis effect for roots of *Echinochloa crusgall* was confirmed.

Table 3 gives the EC_{50} values of 5-fluoro-2-hydroxy butyrophenone against the seedling growth of *Lactuca sativa* and *Echinochloa crusgalli*. The herbicidal activity of the compound against *Echinochloa crusgalli* is weaker than that of Pyrazosulfuron-ethyl, which showed EC_{50} value of 7.18 mg·L^{-1} for the hypocotyls inhibition.

3.2.3. Discussion on the Agricultural Application. The data presented in Tables 1–3 and in Figures 3–4 indicate that 5-fluoro-2-hydroxy butyrophenone is effective in controlling fungus growth and inhibiting plant growth. It should be noted that the test plants, *Lactuca sativa* and *Echinochloa crusgalli*, belong to dicotyledons and monocotyledons, respectively. This means that 5-fluoro-2-hydroxy butyrophenone may have a broad-spectrum activity. There is a potential to develop 5-fluoro-2-hydroxy butyrophenone as a herbicide or an agricultural regulator with good antifungal activity. 5-Fluoro-2-hydroxy butyrophenone can also be considered as a leading compound in devising new fungicides, herbicides, or plant regulators.

Table 2: Antifungal activities of 5-fluoro-2-hydroxy butyrophenone against two pathogenetic fungi.

Pathogenetic fungi	Toxicity regression equation[a]	EC_{50}^{b}/mg·L^{-1} (95% confidence interval)	Chi-square[c]
Valsa mali	$Y = -2.426 + 1.617X$	31.46 (26.53–37.74)	0.652
Coniothyrium diplodiella	$Y = -3.957 + 2.238X$	58.62 (51.38–67.16)	0.675

[a]PROBIT model: Y (probit) = intercept + BX (covariates X are transformed using the base 10 logarithm).
[b]*Cyprodinil* displayed better fungicidal activity against *Valsa mali* and *Coniothyrium diplodiella*, with the EC_{50} values being 10.4 and 10.2 mg·L^{-1}, respectively.
[c]$\chi^2 < \chi^2_{(3,0.05)} = 7.815$ shows that toxicity regression equations obtained can be used for predictions of the inhibition effects.

Table 3: Inhibition of 5-fluoro-2-hydroxy butyrophenone on the seedlings growth of two plants.

Receptor plant species	Toxicity regression equation[a]	EC_{50}^{b}/mg·L^{-1} (95% confidence interval)	Chi-square[c]
Lactuca sativa			
Roots	$Y = -3.379 + 1.732X$	89.36 (75.98–106.64)	2.147
Hypocotyls	$Y = -2.003 + 1.096X$	67.25 (52.66–86.58)	0.501
Echinochloa crusgalli			
Roots	[d]	[d]	[d]
Hypocotyls	$Y = -2.967 + 1.477X$	102.20 (84.56–127.32)	3.933

[a]PROBIT model: Y (probit) = intercept + BX (covariates X are transformed using the base 10 logarithm).
[b]Pyrazosulfuron-ethyl displayed better herbicidal activity against *Echinochloa crusgalli*, with the EC_{50} value of 7.18mg·L^{-1} for the hypocotyls inhibition.
[c]$\chi^2 < \chi^2_{(3,0.05)} = 7.815$ shows that toxicity regression equations obtained can be used for predictions of the inhibition effects.
[d]Because of Hormesis effect, no calculation was done.

4. Conclusions

In summary, 5-fluoro-2-hydroxy butyrophenone was synthesized under mild conditions, and the structure was characterized by the melting point and MS, IR, ^{1}H NMR, and ^{13}C NMR spectroscopy. The bioassay results show that it exhibits potent capabilities against Valsa mali, Coniella dipodiella, and other agricultural plant fungi. It also inhibits the growth of *Lactuca sativa*, a dicotyledon, and *Echinochloa crusgalli*, a monocotyledon. Hormesis effect for roots of *Echinochloa crusgal* was found. There is a potential to develop 5-fluoro-2-hydroxy butyrophenone as an agricultural regulator or herbicide with good antifungal activity or as a leading compound in creating new fungicides, herbicides, or plant regulators.

Conflict of Interests

This paper is the authors' own work, and the research is original. The results have not been published (in any language or medium), and the paper is not considered and will not be offered elsewhere while under consideration for the Journal of Chemistry. All authors have read and approved the revised version of the paper, and due care has been taken to ensure the integrity of the work. No conflict of interest exists in the submission of the revised version. There is no any other possible conflict of interests in the revised version.

Acknowledgments

The authors gratefully acknowledge the financial supports from Scientific Research Program of the Higher Education Institution of Shandong Province (no. J11LC21) and Promotive Research Fund for Young and Middle-aged Scientists of Shandong Province (no. KCCX1-SW-22).

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